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Our training program in breast cancer detection and treatment continues to provide an excellent opportunity to train research fellows who demonstrate an interest in pursuing clinical and technical work relating to breast cancer. Through the dual mentorship system that we have adopted, each of the four current trainees is assigned to both a clinical specialist and a theoretical or research specialist. These complementary yet distinct professional perspectives constitute an invaluable resource throughout the program. Trainees also attend related seminars and conferences as part of their training. Trainee research encompasses a broad range of theoretical disciplines — genetics, biochemistry, electrical engineering, computer science, physiology, and tumor biology — as well as clinical disciplines such as radiology, oncology, pathology, and radiation therapy.

The University of Pennsylvania has developed a broadly-based graduate study program designed to apply theory to clinical practice in developing technology and procedures for the detection and treatment of disease. Throughout this year our work focused primarily upon improving methods of detecting breast cancer through magnetic resonance imaging of tissue, with significant attention paid to the characteristics of the disease at various stages. We have also striven to build upon current general knowledge of the metabolic and genetic parameters of the disease.

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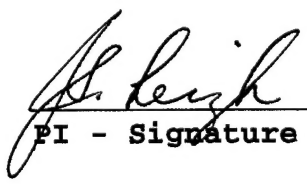

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INTRODUCTION

The training program in Breast Cancer Detection and Treatment continues to provide an excellent opportunity to train research specialists in techniques for clinical and technical work relating to breast cancer. This program has established solid, productive teaching relationships between highly skilled and experienced cancer specialists and qualified recipients. It has also fostered the development of diagnostic and therapeutic technology and the examination of clinical issues concerning this widespread disease.

The dual mentorship system that is in place ensures that each of the trainees in the program are assigned both a clinician and a basic scientist as his or her individual advisors. The trainees benefit enormously from this system, which provides them with two distinct and often complementary sources of insight into the progress of their work and training. Program participants are currently trained in clinical and theoretical procedures by which to detect breast cancer at early stages; they also familiarize themselves thoroughly with the current knowledge of the biology and pathology of the disease and modern therapeutic practice as part of their training. Through their clinical advisor, trainees have access to the resources necessary for clinical research, as well as to the advisor's considerable background in clinical practice and parameters. The extent to which the trainees immerse themselves in clinical research varies according to the area of specialty to which they have gravitated.

The training faculty have been selected to fill either the role of clinician or of theoretical scientist on the basis of their specialization. In our search for qualified advisor candidates, we have sought to exploit existing collaborations between clinic and laboratory in the field of breast cancer research, in an effort to provide an advisory structure conducive to the trainee's academic and professional development.

Our fundamental goal remains to develop new techniques by which to detect and to treat breast cancer, and to enhance those already existing with new knowledge and technological improvements. A significant step towards this end is naturally the thorough training of qualified specialists seeking to gain experience in the theoretical and clinical fundamentals of breast cancer research.

What follows is a brief outline of the available clinical and research techniques in which the four members of the program are being trained, supplemented by a description of the related research undertaken by the trainees in the course of this funding year. We also present the academic status and professional profile of each trainee, as well as a discussion of his or her relationship with both individual advisors and pertinent information about each. Finally, we list the events, activities, and expectations associated with the trainees' participation in the program.

BODY

Magnetic Resonance Imaging (MRI) has established itself on the forefront of medical technology as a non-invasive clinical procedure by which to obtain highly accurate metabolic and oncologic profiles of isolated tissues within the body. The research division of our laboratory dedicated to the use of MRI in the detection and treatment of breast cancer remains extraordinarily active. Significant progress has been made in four areas of MRI research and development: diagnosing cancer, evaluating the local extent of breast cancer, screening high risk populations, and honing techniques for MR-guided breast interventions.

We have made important advances in developing techniques by which to differentiate between benign and malignant enhancing breast lesions using MRI. Such techniques would greatly improve the specificity of breast MRI techniques, given that only about 40% of breast lesions detectable by MRI constitute actual cancer. We will continue to study the kinetics of image contrast enhancement and combine this with our work on breast architectural features in order to provide an improved interpretation model for breast MRI. It is hoped that this work will eliminate the problem of detecting false positives using such a technique.

We are continuing to study the ability of MRI to determine the local extent of breast cancer. This information is essential to the planning of appropriate therapies (lumpectomy vs. quadrantectomy vs. mastectomy).

The program trainees receive comprehensive instruction in the technological principles and procedures fundamental to the research described above. In addition, the trainees are currently engaged in research projects applicable to the broader fields of oncology and pathology. These are introduced below.

Experimental Demonstration of Photon Diffusion Imaging and Diffusive Emission Tomography in Highly Scattering Systems Approximating Breast Tissue

At present there is considerable interest in the use of multiple scattered light in optical tomography, due in part to its potential applications in medicine. While X-ray CT, MRI, and PET have proven to be clinically useful, each suffers from limitations that restrict its application in the widespread screening for cancer in asymptomatic patients. Principal among these limitations are cost and the patients repeated exposure to ionizing radiation in the case of CT and PET. Optical and near-IR wavelengths, at relatively low intensity, suffer no such limitations. Spatial variations in the absorption and scattering properties of a given tissue reveal much about its metabolic state, vascularization, and structure. In addition, mapping the distribution of fluorescently tagged antibodies, in analogy to PET's use of radionuclides, may provide a means of localizing subclinical tumors with great specificity.

A fundamental problem in the reconstruction of images obtained from multiply scattered light is that of mapping variations in the scattering (diffusion) and absorption coefficients. In such highly scattering systems photons migrate in a random walk, experiencing numerous collisions along the path from source to detector. We can regard the transport of scattered light as occurring by means of diffusing waves that are described by integral equations. These integral equations are solved either numerically or by direct inversion in order to reconstruct spatial fluctuations in the absorption and diffusion coefficients of objects embedded in scattering media. In an analogous manner, we also are able to determine spatial variations in fluorophore number densities of fluorescently labeled objects embedded in scattering media.

Our current studies have focused upon experimental validation of our numerical and analytical solutions of these integral equations. Using amplitude modulated, near-IR light sources in continuous wave mode, we record the intensity and phase of the transmitted light as a function of source/detector position. To date, we have successfully reconstructed images of phantoms

whose absorption and scattering properties differ from background in a manner that approximates in situ, tumorigenic tissues. We have also incorporated fluorescently labeled probes into our phantoms and successfully reconstructed not only the object,s spatially dependent absorption and scattering properties, but also the spatial distribution of its fluorophores. Numerical simulations of these experiments, incorporating results from the exact (nonperturbative) solution of the forward scattering problem, have been done to rigorously examine the effects that noise, as well as uncertainties in source/detector position and background absorption/diffusion coefficients, have on the quality of image reconstruction. Additional numerical studies have also been performed to assess the simulated data's correlation to experiment. More recently, we have conducted a series of sensitivity experiments aimed at determining the minimal fluorophore number densities needed for image reconstruction in inhomogeneously absorbing and scattering backgrounds. Our findings suggest that, with additional sources and detectors, these techniques could be of significant clinical value in the widespread screening of subclinical breast carcinoma.

Hadamard Encoded Imaging and Its In vivo Applications

High resolution imaging techniques using noninvasive modalities such as magnetic resonance imaging have been pursued as in vivo cancer screening techniques in an attempt to eliminate the invasive nature of surgical biopsy. The resolution and field of view attainable with magnetic resonance imaging has been limited in the past due to aliasing of the image. We are developing a technique that uses this aliasing to produce high resolution images with larger matrix sizes than are currently available. It is performed in two dimensions, the frequency encoding and phase encoding direction, and the image is allowed to alias in both. The individual, aliased fields of view can be recovered by encoding the spatial information within the plane of the image using Hadamard methods. These images may then be tiled to obtain a composite image with high spatial resolution and a large field of view. This technique is demonstrated using two-dimensional and three-dimensional in vivo imaging of the human brain and breast.

Enhanced Protective Immunity by Recombinant Murine Interleukin-12 is Preceded by a Transient Suppression of Anti-Tumor Immunologic Responses

Our work has focused on the development and understanding of immunologically based cancer vaccines. Studies have included the use of costimulatory molecules and the use of cytokines, both as recombinant proteins and in tumor cell secreted forms, to stimulate anti-tumor responses. I have investigated the immunological basis of interleukin-12's antitumor effects. Interleukin 12 (IL-12) is an immunomodulatory cytokine with potent antitumor, antiviral and antimicrobial effects. Its activities are attributable to its ability to induce Th1 $CD4^+$ T cell differentiation, $CD8^+$ T cell cytotoxicity and NK cell activation. Through its ability to induce the production of IFN-γ by T and NK cells, IL-12 indirectly activates macrophages and induces the production of nitric oxide. IFN-γ also has a variety of effects on other host cells and, relevant to its antitumor effects, IFN-γ upregulates MHC expression, slows cell proliferation and inhibits tumor angiogenesis.

We chose to study IL-12 effects during vaccination with irradiated cancer cell vaccines to avoid confounding factors of tumor growth. We identified a transient immunosuppression of antitumor responses associated with rmIL-12 treatment. rmIL-12 given to A/J mice vaccinated with irradiated SCK mammary carcinoma cells engineered to secrete GM-CSF resulted in significantly better protection from tumor challenges 28 days after vaccination but, unexpectedly, severely compromised host protection 14 days after vaccination. Immune suppression was rmIL-12 dose-dependent and manifest as reduced splenic CTL activity, stimulated cytokine release and ability to reject SCK cells. The period of suppression coincided with transiently reduced splenic T cell mitogenic responses to Con A and IL-2, suggesting that they may be causally related.

We showed that suppressed mitogenic responses associated with rmIL-12 therapy were not restricted to splenocytes from SCK.GM vaccinated, rmIL-12 treated A/J mice but were also found in rmIL-12 treated, vaccinated and naive mice of multiple strains. Suppression appears to be due to impaired immune effector mechanisms rather than impaired host immunization, as evidenced by the enhanced reaction to immunogens when hosts are challenged later after rmIL-12 administration.

We therefore sought to determine the mechanism of this transient immunosuppression and used both DTH (in vivo) and mitogenic (in vitro) responses in C57BL/6 mice immunized with allogeneic HKB cells. Administration of neutralizing antibodies to HKB-vaccinated C57BL/6 mice showed a role for IFN-γ, known to mediate many of IL-12 effects, but not TNFa, a cytokine implicated in IL-12 induced suppression during LCMV infection, and these results were later confirmed in IFN-γ and TNFR

knockout mice. Adherent cells from the spleens of rmIL-12 treated mice were identified as the subpopulation associated with suppressed T cell mitogenic and alloproliferative responses. Further investigation revealed an IFN-γ dependent induction of macrophage derived nitric oxide. Reversion of both in vitro and in vivo suppressed responses was possible by using chemical inhibitors to iNOS. I am currently investigating whether these inhibitors can also reverse suppression in the tumor vaccination model and whether alternative schedules of rmIL-12 administration or costimulation can minimize suppressive side effects.

The following is a list of trainees supported this year, including the period of their appointment and the names of their individual advisors:

Trainees	Period of Appointment	Advisors
Uma Duvvuri	9/1/97 — 8/31/98	John S. Leigh, Ph.D. Susan Orel, MD
Holly Kurzawa	6/1/96 — 5/31/98	William Lee, MD/Ph.D. Yvonne Paterson, Ph.D.
Douglas Fletcher	8/1/97 — 7/31/98	John Glick, MD John Biaglow, Ph.D.
Jeff Souris	9/1/97 — 8/31/98	Britton Chance, Ph.D. Mitchell Schnall, MD/Ph.D.
Erik Shapiro	1/1/98 — 12/31/98	Robert E. Lenkinski, Ph.D. Gilles McKenna, MD, Ph.D.

Uma Duvvuri

Uma Duvvuri is an MD/PhD student at the University of Pennsylvania Medical School. Uma was appointed as a trainee on September 1, 1997. He spent his year completing his medical school coursework and will start in September, 1998 taking graduate level courses. Uma's scientific advisor is John S. Leigh, Ph.D., the Britton Chance professor of radiology and director of radiology research at the University of Pennsylvania. Uma attended the Sixth Annual Sixth Annual Scientific Meeting of ISMRM where he presented two posters.

Holly Kurzawa

Holly Kurzawa completed her training on May 31, 1998. She is a student in the Cell and Molecular Biology Graduate Group. Her primary clinical advisor is William Lee, MD, Ph.D., who is an associate professor at the University of Pennsylvania with attending duties in the department of medicine. His particular expertise lies in the areas of tumor cell vaccines, their incorporation into therapeutic practice, and the regulation of gene expression. Holly has worked closely with him and with Yvonne Paterson, Ph.D., her scientific advisor. Dr. Paterson's specialty is in the regulation of the immune system, particularly biological and biophysical approaches to the regulation of T-cells. Holly attended the Gordon Conference on Cancer in August of 1997 where she presented a poster and "The Department of Defense Breast Cancer Research Program Meeting: An Era of Hope" held in Washington DC, 1997. She regularly attends a seminar series within the Cell and Molecular Biology Group.

Douglas Fletcher

Doug Fletcher was appointed on August 1, 1997. He was a student in the Structural Biology and Molecular Biophysics Graduate Group. His clinical advisor is John Glick, MD, who is the Director of the Cancer Center and Professor in the Department of Medicine, Division of Hemotology-Oncology. He is a medical oncologist with particular interest in breast cancer. His

scientific advisor, John Biaglow, Ph.D., is Director of Oncology Research and has research experience in the area of tumor metabolism and perfusion. The entirety of his training was devoted to developing and implementing a technique that uses a method for aliasing to produce high resolution images with larger matrix sizes than are currently available. The findings were incorporated into his doctoral thesis, which he completed by the end of the academic year.

Erik Shapiro

Erik Shapiro is a graduate student in the Chemistry Graduate Group. He began his training in the program on January 1, 1998. Gilles McKenna, MD, Ph.D. serves as Erik's clinical advisor. Dr. McKenna is chairman of the Department of Radiation Oncology and his primary interests include the identification of molecular and genetic markers in tumors that indicate resistance and/or sensitivity to radio waves. His scientific advisor is Robert E. Lenkinski, Ph.D. Together, they are investigating the use of surface coils, a birdcage coil and a transmit only birdcage coil with surface receive coils. They are currently underway in a plan to determine sodium concentrations in several healthy human volunteers as well as subjects grouped by age.

Jeffrey S. Souris

Jeffrey Souris is a graduate student in the Structural Biology and Molecular Biophysics Graduate Group. Jeff completed his fourth year in the training program on August 31, 1998. During the year he has worked with his two advisors, Drs. Britton Chance and Mitchell Schnall. Dr. Schnall is both a skilled clinician and researcher who has actively pursued the development of NMR techniques for diagnosing breast and prostate cancer. Jeff has been trained in a technique, called Photon Diffusion Imaging, that is potentially useful in gathering imaging data from any number of tissues. This technique holds great promise as a new modality in the early detection of breast cancer, one that does not pose the hazards associated with x-rays. In working with his clinical advisor Jeff has learned about the nature and pathologic parameters of breast cancer, currently available diagnostic tools, and the strengths and weaknesses of these tools in detecting breast disease in its early stages. Jeff attended "The Department of Defense Breast Cancer Research Program Meeting: An Era of Hope" held in Washington DC, 1997.

CONCLUSIONS

We consider the process of education within the training program to be highly mutual. Trainees cull vast amounts of information about the pathology and treatment of breast cancer through discussion with their advisors and regular attendance at seminar series and conferences related to or directly dealing with the disease. In exchange, we expect trainees to disseminate their individual contributions to current knowledge via presentation of their work at conferences and conventions within the scientific community and within the larger community of persons concerned with or affected by the disease.

To be specific, we require that all trainees attend a monthly seminar series called FOCUS, which is hosted by the Group for Women's Health Research and deals with many issues facing today's breast cancer researchers. There are similar seminar series within the Department of Biochemistry and Biophysics and the Department of Cell and Molecular Biology which provide trainees with a solid grounding in the work being done in the broader fields of pathology and oncology. In addition, trainees have traveled to meetings and conferences all over the country to present their work and to elicit feedback from experts in their individual fields. Towards the end of reaching the more general scientific public, trainees have published papers and findings in widely-read scientific journals, newsletters, and brochures. These latter serve the double function of increasing awareness about the training program at the same time that they report on the work of the individual trainees.

The external advisor to our training program is Joann S. Ingwall, Ph.D. She is professor of medicine at Harvard Medical School. Dr. Ingwall's primary obligations to the program consist of offering advice and guidance to the director of the program. In addition, she reviews the progress of all present trainees and suggests possible alterations or improvements to the path of their research.

Our experience thus far with the program has been decidedly positive; we have found it to be an excellent mechanism by which to equip promising researchers with an enormous amount of clinical and technological knowledge relating to breast cancer detection and treatment. We have a strong desire to expand the program within our laboratory to accommodate yet more trainees and to expand the scope of our professional liaisons to include clinicians and research experts from an even greater geographic area.

We continue to search ardently for qualified minority and women candidates and to encourage their interest in the program. Half of our four current trainees are women. The program is promoted to minority candidates by a number of means. We send informational brochures to medical and engineering schools with large minority populations. We also contact persons at the University of Pennsylvania's medical school, biochemical graduate studies office, and engineering school who are qualified to refer interested candidates to us. Through these contacts, we ensure that the program is prominently advertised the minority outreach efforts undertaken by these schools. We keep our contacts informed of scientific workshops, seminars, and training sessions going on within our facility, stressing that interested minority candidates are encouraged to attend. Such events are excellent opportunities for the candidates to interact with the faculty and to be introduced to the specific work we do.

Having obtained the names of potentially eligible minority candidates, we invite them to submit their application to the program and to visit our facility to learn more about opportunities in breast cancer research and about the nature of the training program. In this way, we hope to provide as much information and encouragement as possible to minority candidates to aid them in their decision whether to apply.

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